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Japanese encephalitis in Malaysia: An overview and timeline

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ABSTRACT

Japanese encephalitis (JE) is a vector-borne zoonotic disease caused by the Japanese encephalitis virus (JEV). It causes encephalitis in human and horses, and may lead to reproductive failure in sows. The first human encephalitis case in Malaya (now Malaysia) was reported during World War II in a British prison in 1942. Later, encephalitis was observed among race horses in Singapore. In 1951, the first JEV was isolated from the brain of an encephalitis patient. The true storyline of JE exposure among humans and animals has not been documented in Malaysia. In some places such as Sarawak, JEV has been isolated from mosquitoes before an outbreak in 1992. JE is an epidemic in Malaysia except Sarawak. There are four major outbreaks reported in Pulau Langkawi (1974), Penang (1988), Perak and Negeri Sembilan (1998–1999), and Sarawak (1992). JE is considered endemic only in Sarawak. Initially, both adults and children were victims of JE in Malaysia, however, according to the current reports; JE infection is only lethal to children in Malaysia. This paper describes a timeline of JE cases (background of each case) from first detection to current status, vaccination programs against JE, diagnostic methods used in hospitals and factors which may contribute to the transmission of JE among humans and animals in Malaysia.

1. Introduction

Japanese encephalitis (JE) is a vector-borne zoonotic disease caused by the Japanese encephalitis virus (JEV), which is spread through the bite of a *Culex* spp. mainly *Culex tritaeniorhynchus*. JE is responsible for 30,000–50,000 cases every year and 10,000 deaths in eastern Asia (Schuh et al., 2010). JEV is also known as Japanese B encephalitis (JBV). It was first reported in Japan in 1871 (Go et al., 2014). This virus causes central nervous system (CNS) disease in human and horses. The virus is also responsible for abortion and weakness in swine and fatalities in human and horses. Wading birds and bats act as a reservoir hosts, pigs as amplifying agents, and humans and horses as dead-end hosts (Schuh et al., 2013b). JEV belongs to the *Flavivirus* genus, under the family of *Flaviviridae*. JE cases have been identified in Asian countries including Japan, China, South Korea, Taiwan, Vietnam, Malaysia, India, Burma, Cambodia, Laos, the Philippines, and Sri Lanka. JEV is classified into five genotypes based on the viral envelope gene; JEV (GI), JEV (GII), JEV (GIII), JEV (GIV) and JEV (GV) (Schuh et al., 2013a). All five genotypes have been isolated in the Malaysia-Indonesia region. JE in Malaysia is considered an important disease among children. However, JE is not considered a serious public health problem in Malaysia, except Sarawak (Fang et al., 1980; Sinniah, 1989). There have been four main outbreaks of JE reported in Malaysia over the years: 1974 in Pulau Langkawi; 1988 in Pulau Pinang; 1992 in Serian Sarawak; and 1998–1999 in Perak and Negeri Sembilan (Fig. 1). Some clinical studies in Malaysia showed that JE cases are probably more prevalent than what is reflected in the national figures (Cardosa and Choo, 1991). From a veterinary perspective, Oda et al. (1996) reported that serological examination of animal sera from all the states of Malaysia revealed JE antibodies in pigs, cattle and buffalo (Oda et al., 1996). Similarly, a recent study in companion animals reported a higher seroprevalence rate in dogs, pigs and cattle in Malaysia (Kumar et al., 2017). The true incidence of JE in Malaysia is unknown and almost certainly underestimated (Tan, 1995). Sporadic cases of JE continue to occur in Sarawak, indicative of endemic activity, with an average of greater than 40 recognized cases occurring throughout the year, with peak occurrences from October to December. JE continues to be a public health problem in Sarawak. This study reviewed JEV

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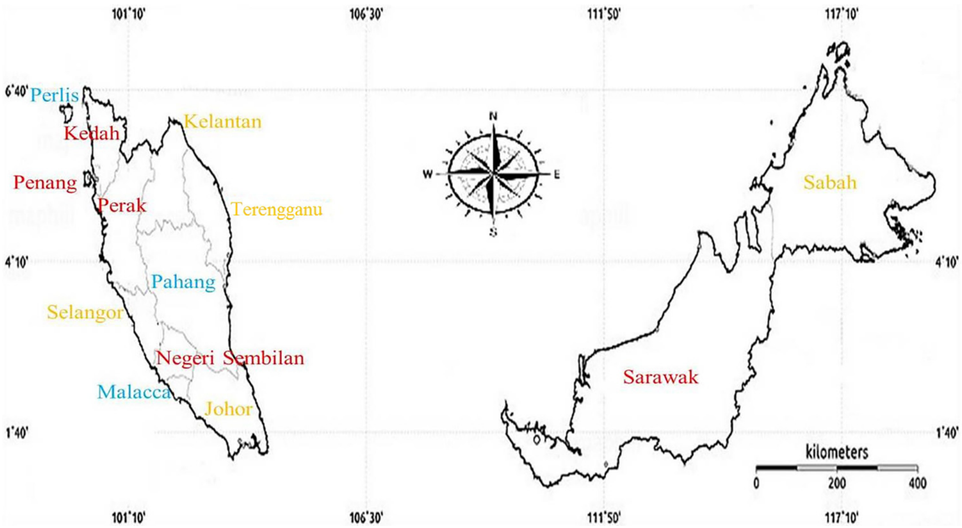

Fig. 1. The figure shows the map of Malaysia. The red color States shows high risk areas for JE where outbreaks have been reported. Yellow color indicates minor human cases were reported and blue color indicates no data available. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

literature from 1940 to 2017, focusing on the JEV scenario in Malaysia, vaccination programs against JE, diagnostic methods used in hospitals and factors which contribute to the transmission of JE among humans and animals in Malaysia.

2. Cohort 1: during 1940–1950

JE was officially reported in 1951 in Malaysia, but cases of encephalitis observed among humans and animals indicate that JEV started spreading much earlier. In Malaysia, JE was initially known as a 'five-day fever' and was common in the human population. The first JE outbreak occurred in 1942, with 37 acute encephalitis cases in a Japanese prison camp at Changi, Singapore (Cruickshank, 1951). Most clinical signs include malaise, headache and fever (38–40 °C). The clinical signs of the prisoners were the same as described in both Indian and British troops at widely separate parts of the Malayan peninsula. The first case was reported in the British wing of the prison hospital and the patient was admitted at the end of March 1942. A huge number of encephalitis cases were reported in the following year in April and May. Eight patients died due to encephalitis. However, there was no isolation of JEV from fatal patients.

Sera samples were collected in the period between 1948–1950 from Malaysia among five different races including Malay, Indian, Indonesian, Burmese, and British and were tested for neutralizing ability against Nakayama strain of JEV. Sixty-four per cent of the 50 sera showed neutralization capabilities against JEV (Paterson et al., 1952). Most of those seropositive for JE were from rural areas in Malaysia. Only the British adult sera showed negative results, as they had spent their lives in South East Asia but had lived in Malaysia for only two years. This indicates that JEV exposure starts early and circulates among the human population in Malaysia during the 30 s.

In 1948, the first horse encephalitic symptoms were observed in Singapore (Hale and Witherington, 1953a). This may indicate that the transmission of JEV started from Singapore then spread to Peninsular Malaysia. However, no other data is available regarding encephalitis outbreak among horses in Singapore during 1948. Fig. 2 shows the overall timeline of JEV infection in Malaysia.

Besides this, Paterson et al. (1952), found JEV antibodies by using complement fixation and neutralizing antibodies against JEV among horses that were imported from United Kingdom and Australia into Malaysia (Paterson et al., 1952). However, JEV seropositive horses in Malaysia from 1948 to 1950 did not show any signs of encephalitis (Paterson et al., 1952).

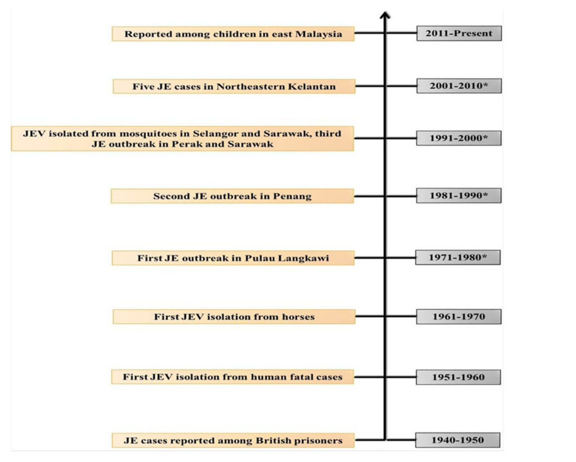

Fig. 2. Time-line of Japanese encephalitis virus infection in Malaysia.

3. Cohort 2: 1951–1960

During the dry season in 1951, an outbreak of encephalitis was reported among recently imported horses in Malaya at the same time as human fatal encephalitis at the British Military Hospital, Kinrara (Kuala Lumpur, Puchong). A British nurse with clinical signs of malaise, weakness pain over her left face, and headache was admitted to the Kinrara British Military Hospital, Puchong, Selangor. However, the nurse died after admission at the hospital. During the autopsy, spinal fluid and brain tissue were collected. A neutropic agent was isolated from the brain cells and identified as JEV Kinrara strain (Paterson et al., 1952). This was Malaysia's first JEV isolation from a human case.

In August 1951, six race horses in Singapore developed encephalitis; however, the horses recovered completely after an illness of 4–9 days (Paterson et al., 1952). The isolation of JEV was unsuccessful from the ill horses' sera. However, blood from infected horses was collected and injected into healthy horses which developed fever and CNS signs after 13 days. Blood and brain tissue were collected from the experimentally infected horses when sacrificed on the seventeenth day after inoculation. The JEV was still not detected and isolated from the experimentally infected horses' brain cells.

In 1952, four JEV isolates were obtained from fatal human cases (Hale et al., 1952). The first case was in Peninsular Malaysia in a 19-year-old British soldier with encephalitis signs. The solider died three days after admission to a Federal military hospital. Brain cells were harvested during an autopsy. The second case was reported in Singapore and the patient was a nine years old girl who suffers from headache and fever. The girl was admitted at the Singapore hospital; however the girl died after three hours of admission at the hospital. The third case was that of a nine year old girl from Singapore with the same clinical sings as the second case. The patient also died following admission to the hospital. The fourth case was a five-year-old boy with critical clinical signs. Clinical signs including clenched teeth and eye deviation were observed. The patient died after admission to the hospital. The isolation of JEV from four fatal cases is important in the history of JEV. This is because the fifth genotype of JEV named as Muar and Tengah strains of JEV were detected from these fatal human cases (Hale et al., 1952; Okuno et al., 1968).

In 1953, around 60 racehorses showed encephalitis during 1950–1953 in Singapore horse farms (Hale and Witherington, 1953b). However, only four horses died. Serological studies among those horses indicated the horses had neutralizing antibodies against JEV antigen. The post-mortem report showed that the brains of the ill horses had lesions. There were no attempts at JEV isolation from the dead horses (Hale and Witherington, 1953b).

Pond et al. (1953), carried out neutralization tests against JEV by using human sera from 284 residents consisting of Malaysian, Borneo and non-Asian residents with long and short residence periods in Malaysia and Borneo (Pond et al., 1953). The life-long residents from peninsular Malaysia showed the highest neutralization rate with 74% compared to residents who spent less than three year which was only 5% (Pond et al., 1953). At the same time, resident from Borneo region showed 67% seropositive for JEV Apart from that, in terms of races in Malaysia, Malays had the highest percentage of neutralizing antibodies with 81% followed by Indians and Chinese with 74% and 63%, respectively. Borneo residents showed only 31.3% JEV seropositive (Pond et al., 1953). Non-Asians showed only five per cent seropositive in the neutralizing test. Concurrently, neutralization tests were carried out among 64 animals including dogs, cows, buffalo, goats, horses, ponies, pigs, zebu and sheep from Kuala Lumpur, Johor, Singapore, and Ipoh. All pig sera recorded high neutralizing indices at 100%, followed by bovine, equines, dogs, and goats with 93%, 90%, 43% and 17%, respectively. However, sheep did not show any seropositivity against JEV (Pond et al., 1953). Horses imported from United Kingdom and Australia, have JEV antibodies within 6–12 months of residence in Malaysia (Hale and Witherington, 1953a).

JEV was isolated from wild-caught *Culex tritaeniorhynchus* in 1956. The mosquitoes were collected from various locations in Malaysia. This shows that *Cx. tritaeniorhynchus* may be a potential vector for JEV in Malaysia (Hale et al., 1957). This is the first isolation of JEV antigen from wild-caught vector in Malaysia.

From the JEV serological studies in 1957 among domestic livestock in Malaysia, pigs, bovid, and goats showed 90%, 70% and 25% neutralizing antibodies for JEV, respectively (Smith, 1958). This may indicate that pigs acted as an amplifying host during the early 50s. Simultaneously, Smith (1958) also reported higher JEV antibody titers among human donors from coastal rice plain areas as compared to other areas like narrow rice valley, coastal swamp, forest fringe and mountains.

4. Cohort 3: 1961–1970

The serological studies against arboviruses among residents in Malaysia were also reported by Pond (1963). The sera were collected from residents of a rubber plantation near Kuala Lumpur. Most residents in this area were Tamil Indians who had migrated from Tamil Nadu during their youth. Seroprevalence for JEV was higher once compared to other arboviruses (Pond, 1963).

Concurrently, encephalitis cases were observed among horses in Ipoh in 1965. Most of the horses showed clinical signs like pyrexia with 42 °C body temperature and neurological signs (Kheng et al., 1968). A horse that died of JE was imported from Singapore in 1965. Post-mortem examination of the horse revealed that the cerebral vessels were highly congested. The brain tissue was collected during autopsy and JEV antigen was isolated from the brain. This was the first animal JEV isolated in Malaysia.

The epidemiology of arbovirus studies in Sarawak were carried out in Kampung Tijirak which is near Land Dayak village. Cohort studies started from December 1962 to January 1963, April to May 1964 and September to December 1966. These studies focused mainly on arbovirus antibodies in humans, animals, mosquitoe population and isolation of arboviruses from the mosquitoes (Simpson et al., 1970b). In serological studies, dogs, ducks, birds, geese, rodents, bats, pigs and fowls were tested. Dogs showed higher seroprevalence rate of 84% in comparison to other animals, including pigs, birds and ducks, which showed 46%, 18% and 6% respectively. In terms of isolation of arboviruses, 55 arboviruses including JEV, Tembusu virus, and other arboviruses were isolated from varying mosquito species like *Cx. gelidus*, *Cx. tritaeniorhynchus*, *Mansonia uniformis*, *Mansonia* spp., *Anopheles* spp. and other species (Simpson et al., 1970b). In a continuation of the study with virus isolation from mosquito populations from Kampung Tijirak, another 16 JEV strains were isolated mainly from *Culex gelidus* and *C. tritaeniorhynchus* (Simpson et al., 1970a).

Alongside, a mosquito population study in Tijirak, Land Dayak village was carried out to determine the mosquito populations in different areas. The mosquitos were collected from villages, scrubs, and paddy areas (Hill, 1970). The study found that *Cx. tritaeniorhynchus* was the primary vector biting humans and pigs. Apart from that, is was also documented that *Cx. tritaeniorhynchus* was mainly found in villages, followed by paddy cultivation areas as a primary breeding site (Hill, 1970).

5. Cohort 4: 1971–1980

5.1. Outbreak of Japanese encephalitis in Pulau Langkawi in 1974

Pulau Langawi is located at 6°21′N 99°48′E 30 km near the mainland coast of north-western Malaysia and is part of the state of Kedah, which is adjacent to the Thai border. The first JE outbreak reported in Malaysia was reported in Pulau Langawi. Initially nine cases were reported from Pulau Langkawi, which was reported to the district hospitals at Kangar, Perlis and Alor Star, Kedah (Fig. 3). Two cases out of nine were excluded from this JE report due to comorbid bacterial meningitis and bronchopneumonia infection (Fang et al., 1980). However, three additional cases with JE clinical sign brought the total number of cases reported to ten. All the cases were confined to Pulau Langkawi. One patient from Palau Tuba was studying at a residential school in Pulau Langkawi (Fang et al., 1980). There were no other JE cases or encephalitis symptoms reported in Pulau Tuba. The investigation of patient included risk factors like household, surroundings, sex-age distribution, previous movements of the patients to onset of the disease, and animals present near the household. However, the study focused on the movement of animals in household to determine amplifier host for JE cases. Pig farming was not observed in this area due to the Muslim community. The clinical signs and symptoms were observed among the patients; all cases reported that the patient had high fever above 40 °C. In terms of age and sex, two cases were below 5 years old; 2 cases between 6–10 years old; 3 patients were between 11–20 years; 2 cases were between 21–40 years; and 1 case was 40 or above (Fang et al., 1980). Majority of JE cases reported were in males because they are outside late in the evening and are more exposed to JE virus-infected mosquitoes. Mostly, water buffaloes, chickens, ducks, cats and dogs are observed in JE reported areas. Fang and his colleagues also investigated the mosquito species present in the areas. Various species of mosquitoes were identified, including *Culex annulus, Cx. bitaeniorhynchus, Cx. fuscoecphalus, Cx. pseudovishnui, Cx. sinensis, Cx. sitiens, Cx. tritaeniorhynchus*, *Aedes- albopictus, Armigeres subalbatus* and *Anopheles-*

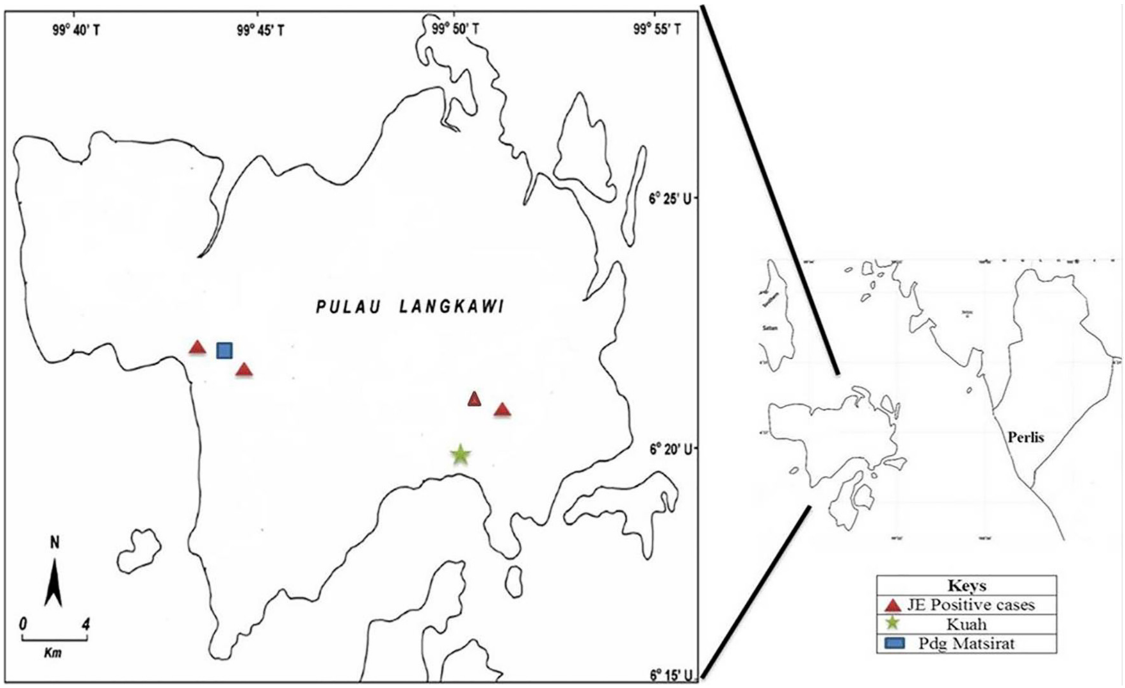

Fig. 3. The map of Langkawi shows the case of JE in Kuah and Padang Matsirat.

barbirostris, korwari, philippenensis, and *vagus* in JE confirmed areas (Fang et al., 1980). The outbreak was described based on clinical reports, serological determination, and the presence of mosquito species. However, the amplifier was not reported in this study and is still unknown. The most common animals found in this area were water buffaloes. However, villagers did not consent to conduct serologic examination on the buffaloes (Fang et al., 1980). The previous studies show that some bovine species have shown high percentage of JE antibodies in southern and eastern Indian areas (Carey et al., 1969; Rodrigues et al., 1976). However, bovine species did not really experience viremia and were not directly involved in JE transmission.

6. Cohort 5: 1981–1990

6.1. Outbreak of Japanese encephalitis in Penang-1988

In Penang, nine JE cases were confirmed, with four fatal cases (Cardosa et al., 1995). However, there are no other data regarding the background and place of victims during JE outbreak in Penang.

7. Cohort 6: 1991–2000

7.1. Serological studies among children in Penang

Serological studies were carried out to determine the presence of JEV antibodies among children after a JE outbreak in Penang. One hundred and ninety-five children with central nervous system (CNS) symptoms and 482 children without CNS symptoms were admitted into the pediatric ward of Penang Hospital between 1990 and 1992. Out of 195 children, only five children had positive JE IgM antibodies. At the same time, from 482 non-CNS cases, only 2 had JE IgM antibodies (Cardosa et al., 1995).

7.2. JEV isolated from mosquitoes in Selangor in 1992

In May 1992, a human JE case was reported in Kampong Pasir Panjang in the district of Sabak Bernam in Selangor (Vythilingam et al., 1993). Vytilingam and colleagues collected samples of the female mosquitoes in Sabak Bernam from May to November 1992 (Vythilingam et al., 1995). A total of 16 JEV strains were isolated from *Cx. tritaeniorhyncus* (3 pool samples), *Cx. vishnui* (4 pool samples), *Cx. bitaeniorhynchus* (3 pool samples), *Cx. sitiens* (1 pool samples), *Aedes butleri* and *Ae. albopictus* (1 pool sample) and *Cx* spp. mixture (3 pool samples) (Vythilingam et al., 1994, 1995). At the same time, JEV was also isolated from pooled samples of pf *Ae. butleri*, *Ae. albopictus*, *Cx. bitaeniorhynchus* and *Cx. sitiens* (Vythilingam et al., 1995).

Simultaneously, Vythilingam also reported isolation of 45 JEV strains from mosquito pools including *Cx. tritaeniorhynchus*, *Cx. gelidus, Cx. fuscocephala*, *Ae. hutleri*, *Cx. quinquefasciatus*, *Ae. lineatopennis*, and *Ae. cancraedes* collected from Sungai Pelek, Sepang district, which is near the Bukit Pelanduk, Negeri Sembilan pig farming area, between January 1992 and December 1993 (Vythilingam et al., 1997).

7.3. Serian, Sarawak-1992

An outbreak in Serian, Sarawak was reported in 1992 with 10 cases and 3 deaths (International Society for Infectious Diseases, 1999f) (Fig. 4). However, there are no other data available regarding outbreak in Serian, Sarawak. Some studies indicated that JEV and antibodies

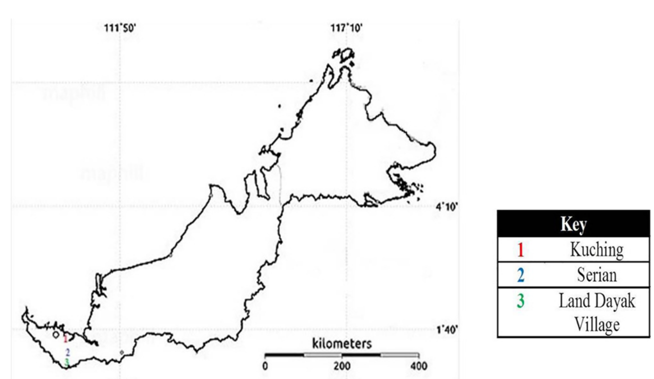

Fig. 4. Map of Sarawak; there places were reported with human JE cases, Kuching, Serian and Land Dayak Village.

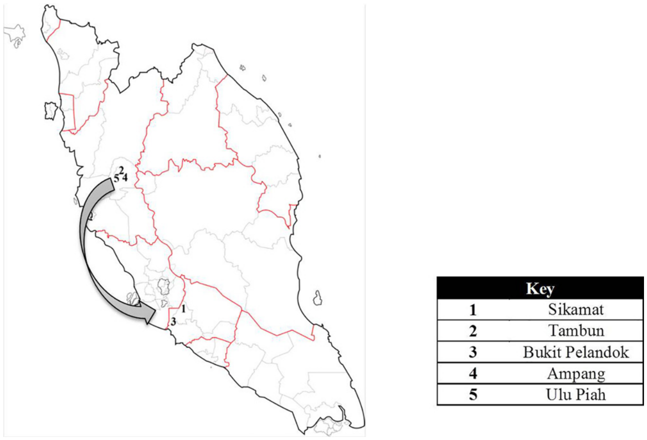

Fig. 5. Spread of JEV from Perak, Tambun to Negeri Sembilan which is almost 267 km away.

were circulating in the 1960's before the outbreak in 1992 (Simpson et al., 1970b; Bowen et al., 1975).

7.4. Perak and Seremban-1998–1999

JE outbreaks in Perak and Seremban are important outbreaks in the history of JEV and Nipah viruses in Malaysia. Both viruses originated from Perak and then spread to Seremban (Chua, 2003) (Fig. 5). The Bukit Pelanduk, Seremban pig farm was once the largest pig farm in the country (Amal et al., 2000). Bukit Pelanduk pig farms had workers supplemented by migrant workers from Bangladesh, India, and Nepal. They raised pork for local consumption and export to Singapore and Hong Kong (Ng et al., 2009). Tambun, Perak has also become famous for pig and chicken farming. This practice continued until the turn of the century when JE smashed into this district. Before the JE outbreak in Perak, it was the second largest pig producer with 318 farms and a swine population of 609,091 in 1998. However, after the outbreak, Perak fell to 387,438 pigs in 190 pig farms, mainly in Kinta valley, with 77 farms within a 10-km radius from Ipoh. Three places in Kinta district, including Tambun, Ampang and Ulu Piah had the maximum number of JE cases in Perak (International Society for Infectious Diseases, 1998a). In November 1998, a pig farmer was the first victim of JE outbreak in Perak. The victim showed clinical signs of high fever (40–41 °C), headache, and drowsiness, followed by coma before sudden death. Cerebrospinal fluid (CSF) samples from the victim were sent to the Institute for Medical Research for confirmation of JEV infection (International Society for Infectious Diseases, 1999a). Serological test was used to detect IgM in JE cases in early 1999. Beside this, the Perak Veterinary Services Department reported that there were no cases of animals which were seropositive for JEV. Interestingly, in 1999 an outbreak of Nipah virus was first thought to have been due to JEV, and indeed there were some confirmed cases of JE before the Nipah outbreak, leading to a local program of vector control and JE vaccination. However, the occurrence of cases of encephalitis in vaccinated individuals and the death of significant numbers of pigs indicated that another agent was responsible and later found out to be Nipah virus (Mackenzie et al., 2007). In the mid-2000s, pig blood samples were collected from 160 farms and sent to the Veterinary Research Institute (VRI) to test using enzyme-linked immunosorbent assay test (ELISA). The positive JEV samples were sent to the Australian Animal Health Laboratory in Geelong, Australia for a serum neutralization test (Arkib, 2000; International Society for Infectious Diseases, 1999b). Table 1 show timeline of JE cases in Perak and Seremban.

8. Cohort 7: 2001–2010

8.1. Kelantan (2006)

Five JE cases were identified in separate villages in north eastern state of Malaysia; Kelantan (International Society for Infectious Diseases, 2006). In the first case, a 13-year-old girl died of JE in Tanah Merah (International Society for Infectious Diseases, 2006). The girl suffered from high fever, headache and discomfort, all symptoms indicated towards JEV infection. At the same time, another girl 13-year-old from Tanah Merah died due to JEV infection and her father and 5-year-old brother were also confirmed to have JEV infection at the Raja Perempuan Zainab II Hospital in Tanah Merah, Kelantan. The firth case was a 27-year-old woman who was infected with JE virus. The JE was last reported in Kelantan in 1995; however, data is not available in this case (International Society for Infectious Diseases, 2006).

9. Cohort 8: 2011–2017

9.1. Pulau Penang and Sarawak (2014)

Three cases of JE were reported in Penang in 2014 from different areas. Two cases were from George Town and Bagan Jermal in north Seberang Perai. The third case was reported in Tasek Gelugor. There are no pig farms in George Town and Bagan Jermal. The Penang Department of Veterinary services collected blood samples from 20 pig farms in Kampung Selamat, Tasek Gelugor which are located within 1 km radius from the school where the 12-year-old boy was confirmed of JEV infection (Chu, 2014). However, test results were negative from 200 blood samples from 20 pig farms in Kampung Selamat and Seberang Perai (Chu, 2014).

In 7th July 2014, 17 JE cases were reported nationwide consisting of 8 JE cases from Sarawak, 4 cases from Sabah, 3 cases from Penang, and one case each from Selangor and Kelantan. Overall four were fatal (International Society for Infectious Diseases, 2014). Deaths reported in Sabah due to JE involved a two-year-old child from Kota Kinabalu and another from Tuaran (Malay, 2014). Overall 47 and 36 JE cases were reported nationwide in 2014 and 2015, respectively (World Health Organization, 2017).

In 2016, three JE cases were reported in Negeri Sembilan, Jelebu and Kuala Pilah (Nur Aqidah Azizi, 2016). In 2017, WHO reported that Malaysia had 59 JE cases documented in 2016 (World Health Organization, 2017). At the same time, seroprevalence study among companion animals and livestock in Malaysia was conducted in 2017. Dog's showed a higher seroprevalence rate of 80% followed by pigs and cattle with 44.4% and 32.3%, respectively (Kumar et al., 2017)

10. Diagnostic methods used in Malaysia

Molecular assay based detection of JEV antigen is widely used in Malaysia. Blood samples are used for the detection of JEV antigen. In veterinary perspective, the animal sera were used in detection of JEV. However, a study in India showed that the sensitivity of PCR for detection of JEV in the human cerebrospinal fluid (CSF) was 65% (Kabilan et al., 2004). Blood and CSF samples were tested for viral RNA confirmation. However, in Malaysia, CSF is used for ELISA (detection of JE virus-specific IgM), haemagglutination-inhibition or virus neutralization assays tests. Nevertheless, patients must not have any history of recent yellow fever vaccination, meaning that cross-reactions to other *Flaviviruses* are excluded. Detection of specific JE-IgM in serum and CSF is the most ordinarily used method for diagnosing JEV in suspected cases. Typically, in 75%–90% of JE cases, specific JE-IgM are detected within 10 days after illness. Lowry et al. (1998), reported that detection of specific JE-IgM in CSF revealed about 30% to 67% negative results in every sample (Lowry et al., 1998). However, by comparing the results reported by Chanama et al. (2005), patients from Thailand have shown

Table 1
Time Line of JE cases in Perak and Seremban.

Dates	Cases
February to October, 1998	*Perak:* - Total of 18 JE cases were reported, five cases of deaths. The 18 cases consist of pig buyer, pig farm workers, owner and their family members (Siang, 1999).
November, 1998	Perak: - The first JE outbreak case was reported on 4th November, 1998. - 15 cases with 4 deaths (International Society for Infectious Diseases, 1998b).
December, 1998	Perak: - Vaccination programs were introduced for high risk groups including pig farm workers and handlers (International Society for Infectious Diseases, 1998c).
January, 1999	*Negeri Sembilan:* - The first JE suspected case was reported on 4th January, 1999 in Sikamat, Negeri Sembilan. Seven cases were suspected to be JE; three cases were confirmed as JE with one death. - 34 people from Sikamat, Seremban were admitted to the Seremban Hospital due to clinical symptoms of JE (International Society for Infectious Diseases, 1999c). - JE cases were reported in Kampung Wong Seng Chow, Sikamat and surrounding places. A 13-year old girl who worked in a pig farm in Kampung Wong Seng Chow was a victim of JE. - Veterinary Research Institute detected JEV in blood samples of pigs collected from Negeri Sembilan (International Society for Infectious Diseases, 1999d). - JE vaccination programs were introduced for Seremban residents, especially children under 12 years from Bukit Pelandok. *Perak:* - Pigs in Ipoh including Tambun, Ampang and Ulu Piah were vaccinated against JE (International Society for Infectious Diseases, 1999d).
February, 1999	*Perak:* - 25 JE cases were reported in Ipoh. *Negeri Sembilan and Selangor:* - Five deaths were reported in Negeri Sembilan and one case from Selangor. *Terengganu:* - 14-year-old boy from Kula Terengganu, Terengganu was confirmed to have JE (International Society for Infectious Diseases, 1999e).
March, 1999	*Negeri Sembilan:* - Pigs from Kampung Sungai Nipah and Bukit Pelandok were killed to prevent JE transmission. - Three primary schools were closed in Negeri Sembilan. - More than 30 residents from Kampong Sungai Nipah in Bukit Pelandok were moved. - Ten people who lived near pig farms died in Negeri Sembilan. - Sarawak vaccinated all pigs within the area of JE confirmed cases. - By March 1999, 107 JE suspected cases with 30 confirmed and 47 fatal outcomes were recorded. - 7 JE suspected cases in Sikamat, Negri Seremban (2 confirmed, 5 fatal). - 74 JE suspected cases in Bukit Pelandok, Negri Seremban (17 confirmed, 27 fatal) (International Society for Infectious Diseases, 1999d). *Perak:* - 26 JE suspected cases in Kinta, Perak (11 confirmed, 15 fatal).
April 1999	*Perak:* - 6th April 1999, 26 JE suspected cases and 11 confirmed JE positive cases in Perak. - Fifteen death cases, five cases were confirmed as JE (Siang, 1999). *Negeri Sembilan:* - 198 JE suspected cases of which 34 cases were positive for JE. - 68 death cases of which 19 cases were positive for JE (Siang, 1999).

that IgM detection in CSF indicated positive results as compared to the serum samples (Chanama et al., 2005). The CSF samples can be 100% positive by day 7, but the serum samples do not show positive results until day 13 (Mackenzie et al., 2007). JE infection may be asymptomatic and can concurrently occur with other infections antigens causing central nervous system symptoms like West Nile encephalitis (Sejvar, 2007). Sometimes serological tests for JE infection may not be correct in indicating JE, with false positives caused by crossing with other *Flavivirus* (Sejvar, 2007).

11. JE vaccination programmer in Malaysia

The JE vaccination was introduced in July, 2001 to reduce the number of JE cases in Malaysia (Wong et al., 2008). However, the vaccination was only practiced in Sarawak. The formalin-inactivated mouse derived JE vaccine (Biken, Japan) is used in Malaysia (Impoinvil et al., 2013). The vaccine is given at 9 and 12 months followed by boosters at 18, 54, 96, 132 and 180 months (Wong et al., 2008; Impoinvil et al., 2013) (Fig. 6).

12. Possible transmission of JEV in Malaysia

12.1. Pig farms development

Pigs are considered as one of the amplifying agents for JEV. The development of pig farms can increase the risk of JE cases. In Malaysia, the pig population reached 1,471,308 head in 2017 and Peninsular Malaysia had a population of 1,364,583 (Jabatan Perkhidmatan Veterinar, 2018). However, most pig farms in Malaysia are located in areas far from residents, schools and markets. Pig farm workers have high risk for JEV infection. The transmission of JEV in pig populations is not dependent on higher populations or large numbers of pig farms, and JEV still can infect pigs even if the population is small (Rosen, 1986; Ting et al., 2004). Ricklin et al (2016), reported that JEV can be transmitted via oronasal secretion. This causes foremost influence on the JEV transmission in temperate countries which have short mosquito seasons.

12.2. Paddy production

Paddy field areas are common places for mosquitos to breed, especially *Culex* spp. and *Anopheles* spp. Some studies indicate that rice fields in Korea are linked to mosquito population and subsequent JE cases (Richards et al., 2010; Masuoka et al., 2010). Amerasinghe and

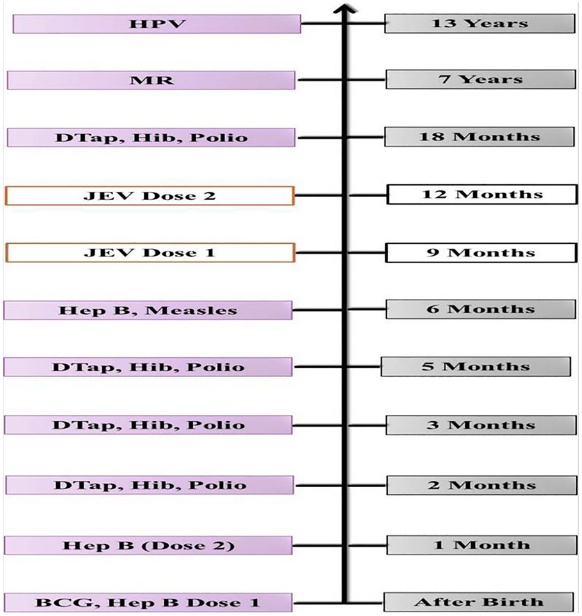

Fig. 6. The figure shows immunization schedule for children in Malaysia. Immunization against JE is implemented only in Sarawak (Luu, 2014). HPV: Human Papilloma Virus Vaccine, MR: Measles Rubella Vaccine, Hib: Haemophilus Influenzae Type B Vaccine, DTap: Diphtheria, Tetanus, and Pertussis Vaccines, Hep B: Hepatitis B vaccine, BCG: Bacillus Calmette–Guérin vaccine.

Indrajith (1994), documented that the larval populations are low after transplanting rice seedlings and the larval population will peak or decline after plants reach a height of 60 cm due to extensive cover of growth paddy plant. *Cx. tritaeniorhynchus* is the dominant mosquito species in rice fields in Peninsular Malaysia as well as *Cx. gelidus, An. peditaeniatus, An. sinensis, Cx. bitaeniorhynchus* and *Cx. pseudovishnui* (Abu Hassan et al., 2010). Countries like Bangladesh, Cambodia, Indonesia, Laos, Myanmar, North Korea, and Pakistan have seen an increase in JEV transmission due to rice farming and a growing population, increased number of pig farms, and lack of reconnaissance and vaccination programs against JE (Erlanger et al., 2009).

12.3. Migratory and wild birds in Malaysia

Migration by migratory birds can be categorized into two which are Northern and Southern Hemispheres. The migratory birds' cycles are dived into: (I) Breeding time May to August; (II) Southward migration time August to November; (III) Non-breeding time December to February; and (IV) Northward migration time March to May (Bamford et al., 2008) (Fig. 7). Important locations for migratory birds landing in Malaysia are found on the west coast of Peninsula Malaysia and the eastern state of Sabah on Borneo. Pulau Bruit in Sarawak has a significant number of migratory birds landing during non-breeding time. There is also Kapar Power Station in Selangor and Pulau Tengah Johor on the west coast of Peninsular Malaysia which is popular for migratory bird landings. Papar is another place in Sabah for migratory birds landing. Most birds are shorebirds which are potential sources for monitoring *Flaviviruses* including JEV and WNV. A majority of countries in the East Asian Australasian flyway are endemic with JEV. Most migratory bird landing areas have water bodies, especially in Kapar Selangor which has higher water bodies for mosquito breeding.

Birds belonging to *Ardeiidae* including herons and egrets are considered reservoirs of JEV (Bhattacharya and Basu, 2014). There are three isolations of JEV from species such as Black-crowned night heron (*Nycticorax nycticorax*), Plumed egrets (*Egretta intermedia*), and Little egrets (*Egretta garzetta*) (Mackenzie et al., 2007). These birds forage in paddy fields that are also JE vector breeding sites. In Malaysia *Ardeiidae* birds such as little egret, black crowned night heron and cattle egret are habitats in paddy cultivation areas like Parit Buntar and Tanjong Piandang, Perak, Malaysia.

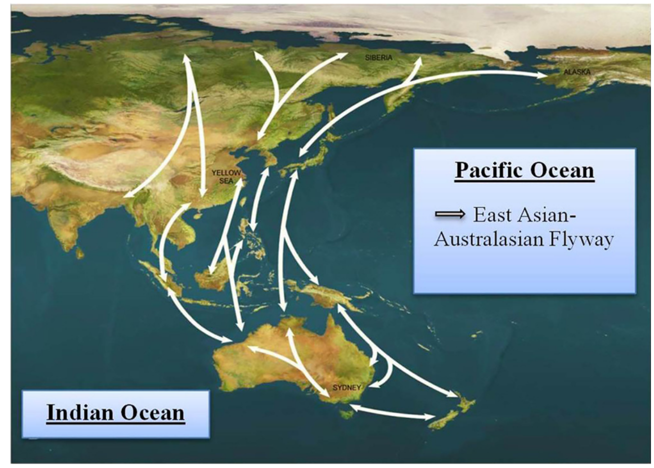

Fig. 7. A Flyway of migratory birds in East Asian-Australasian route (Bamford et al., 2008).

12.4. Rubber plantation

Rubber plantations are considered one of mosquito breed sites. Dengue is epidemic in rubber plantations areas (Tangena et al., 2016). Rubber plantations provide breeding sites in latex-collection cups, tree holes, and water storage tanks (Thammapalo et al., 2009; Paily et al., 2013). There is no *Culex* spp. population documented in rubber plantation areas in Malaysia. However, in Thailand, mosquito populations are high in rubber plantations and forest areas. High populations of *Cx. vishnui* was found in Kancanaburi and Khon Kaen rubber plantations (Sumodan et al., 2015).

12.5. Bats population

Bats are important wild animal involved in the transmission of viruses, especially Ebola virus, Rabies virus, Lyssavirus, Marburg virus, Nipah virus, Hendra virus and JEV (Tiawsirisup et al., 2012). There are four JEV isolations from bats in Yunnan Province, China, two of which are from Leschenault's rousette (*Rousettus leschenaultia*), a fruit bat in 1989 and a little tube-nosed bat (*Murina aurata*), in 1997(Wang et al., 2009). Bats are inclined to roost in trees, caves and roofs in residential areas and can be close to rice fields and pig farms. These areas provide abundant avenue for JEV transmission like mosquito-bat-mosquito to humans or other animals. JEV can induce viremia in bats that lasts long enough for transmission of the virus into mosquitoes. Some bats, especially *Preropus* spp. are able to cross between peninsular Malaysia Sumatra and Australia to New Guinea (Breed et al., 2006). Isolation of NiV from *P. hypomelanus* in Thailand showed similarities NiV-My isolated from *P. hypomelanus* in Tioman Island, Malaysia, which is about 960 km from Thailand National Park (Wacharapluesadee et al., 2016).

12.6. Climate change

The impact of climate change will lead to arbovirus transmission throughout the mosquito life cycle (Impoinvil et al., 2012). The El Niño and La Niña-Southern Oscillation (ENSO) have foremost impact on climate change in the tropics, which highly influence transmission of arboviruses (Philander, 1990). When temperature increases, the rate of abrovirus infection in mosquitos will increase and the extrinsic incubation time will reduce (Takahashi, 1976). This climate change also has an impact on JEV transmission since other members of the *Flavivirus* genus, like West Nile and dengue infection have shown that change in climate is an important driving force (Tipayamongkholgul et al., 2009; Paz, 2015). Some studies have shown that transmission of JEV to humans is much higher during high ambient temperature with low rainfall (Mogi, 1983). This can be explained by three core factors which are; a) increased virus multiplication in mosquito salivary glands; b) higher survival of immature mosquitoes through reduced maturation time as a result of rainfall and high temperatures; and c) reduced losses of aquatic phases as a result of low precipitation (Bi et al., 2003, 2007; Hsu et al., 2008; Impoinvil et al., 2011). Impoinvil et al. (2013) found that 60% vaccination effectiveness would result in larger than 30% decreased risk of JE cases in Sarawak after monitoring the climate. This is the first estimation of JE reduction over vaccination by including climate interannual variability. This analysis also endorsed that vaccination has significantly cut JE risk in Sarawak but this value may be overrated if climate factors are omitted (Impoinvil et al., 2013).

12.7. Mosquito population

Vectors play an important role in the transmission of arboviruses and the absence of mosquitos is able to prevent the transmission of arboviruses. Several species of mosquitoes are involved in JEV transmission; however *Cx. tritaeniorhynchus* is a primary vector for JEV in Asian countries (Burke and Leake, 1988; Endy and Nisalak, 2002). *Cx. quinquefasciatus* and *Cx. tritaeniorhynchus* are widely distributed mosquito population in Malaysia, and Selangor has a higher population of *Cx. quinquefasciatus* (Low et al., 2013) and both species are important in transmission of JEV. Some countries like Australia have reported that *Cx. annulirostris* is a primary vector for JEV (Mackenzie et al., 2002). In Malaysia, *Cx. gelidus* is an important vector in the transmission of JEV among pigs (Simpson et al., 1976). JEV vectors mostly have zoophilic feeding behavior or feed on animals as primary source of blood. Most research has shown that mosquitoes feed on cattle, pigs, goats, deer, antelopes and gazelles, animals classified as cloven-hoofed ruminants (Mitchell et al., 1973; Reuben et al., 1992; Khan et al., 1997; Mwandawiro et al., 2000). The feeding rate of mosquitoes on birds and humans is relatively low compared with cloven-hoofed ruminant type animals (Reuben, 1971). In humans, anthropogenic behaviors increase the chances of exposure to JE vectors. During summer season people sleep outside at night, increasing the risk of exposure to JEV. Besides this, people that work at night in companies, farms, and security guards in contracting areas also have high risk of exposure to JE vectors. *Cx. tritaeniorhynchus* is active at night and other JE vector including *Cx. annulus*, *Cx. vishnui* and *Cx. pseudovishnui* primarily feed and rest outdoors (Mitchell et al., 1973; Reuben, 1971; Kanojia and Geevarghese, 2004). However, some JE vectors are still found indoors, as observed during JE epidemic seasons (Mitchell et al., 1973). The experimental infection proved that the *Cx. tritaeniorhynchus* is able to transmit JEV early with post infection contingent on prevailing temperatures (Impoinvil et al., 2012) and high competent JE vector especially *Culex* spp. is able to transmit the JEV with low dose of virus. The virus replication site in mosquitoes, the salivary gland, can be high as 104.2 SMIC-LD50/1 mL of saliva and virus diluents (Takahashi, 1976). The female mosquitoes are able to transfer the JEV to their progeny after infection with the virus and the female progeny can also transfer to different hosts during blood sucking.

12.8. Other arthropods

JEV has also been isolated from other blood sucking arthropods like *Forcipomyia taiwana* and *Culicoides* spp. in China (Wang et al., 2007). However, the role of other arthropods in the transmission of JEV has not been determined. This shows that other arthropods may also be involved in the transmission of JEV among humans and animals.

12.9. Role of other vertebrates

Animals like cattle, water buffalo, sheep, goats, dogs, chicken, ducks, cats and horses are common in Malaysia. JEV is able to infect cattle, water buffalo, sheep, goats, dogs, raccoons, mongooses, and chickens; however, the roles of these animals are unknown (Peiris et al., 1993; Ohno et al., 2009; Saito et al., 2009). These animals are involved directly in transmission of JEV and are considered ‘dead-end’ hosts. However, some animals play indirect roles in JEV transmission. For example, cattle play an indirect role (zooprophylaxis) due to the fact that *Cx. tritaeniorhynchus* are more attracted to cattle than pigs (Mwandawiro et al., 2000). Cattle provide a significant amount of blood source for mosquitoes required for passive zooprophylaxis (Mwandawiro et al., 2000). Some research has shown that zooprophylaxis hosts are separated from human populations and mosquito breeding sites, which is able to increase the vector population. Besides this, cattle and goats are considered better indicators of JEV transmission than pigs, as cattle seroconvert less readily to infection with JEV. Seroprevalence detection in cattle may reflect intense and repeated infection, which may be an indicator of JE ‘spill-over’, whereas porcine seroprevalence is an indicator of any JE activity in a given area (Impoinvil et al., 2012).

13. Reconsideration of JE control in Malaysia

13.1. Insecticides

Control of mosquito vector has long been a serious part of the global policy to supervise mosquito-associated diseases. Mosquito control programs widely use insecticides. These programs assume that large numbers of mosquitoes can be eliminated which can in turn interrupt JEV transmission. The wide usage of insecticides like pyrethroids, organophosphates and carbamates have limited role in the control of mosquito vectors. The effectiveness of these insecticides in controlling vector-borne diseases is still questionable. This is because the insecticides only target adult mosquitoes and not younger mosquitoes or larvae (Wang et al., 2014; Leong et al., 2018). Although adult mosquitoes would be killed, the young and larvae are protected from the insecticide and in a few days they develop into adult mosquitoes to replace their dead comrades. Additionally, the use of heavy pesticides in rice fields will increase resistance in mosquitoes (Karunaratne and Hemingway, 2000). This deadly pesticides exposure could prompt the production of detoxification enzymes in mosquitoes to destroy the pesticides (Rivero et al., 2010). Indoor mosquito spraying using dichlorodiphenyltrichloroethane (DDT) is also considered ineffective against JEV vectors due to the fact that vectors like *Cx. tritaeniorhynchus*, *Cx. quinquefasciatus, Cx. gelidus, Cx. bitaeniorhynchus, Anopheles subpictus* and *An. vagus* are usually found outdoors and not indoors (Reisen and Milby, 1986).

14. Viewpoint of JEV in Malaysia

JE cases in Malaysia are still under control among children in Malaysia except Sarawak. In Malaysia, pig farms are far away from residential areas in order to avoid the smell coming from the farm and also due to religious concerns. Most of the pig farms were relocated far away when the farms become closer to the residential areas. This makes the chances of JEV transmission; pig-mosquito-human cycle tremendously reduced. Paddy cultivation areas are also high risk areas for JEV transmission as reported earlier due presence of *Culex tritaeniorhyncus,* a primary vector for JEV in paddy cultivation areas (Dhakal et al., 2012). When paddy cultivation areas and pig farms are close to each other, the transmission of JEV is higher. In Malaysia, pig farms and paddy growing areas are not close to each other due to the involvement of Malays in paddy production. Pig farms and paddy cultivation are always separated and pig farms are always isolated in deeper areas in

Malaysia. But other amplifying hosts like little egrets and plumed egrets are frequently observed in paddy cultivation areas in Malaysia. JE is still detected among children in Malaysia mainly in Sarawak. In Sarawak, the source of JEV was believed to be from wild boars. Most people in Sarawak keep wild boars for meat. This led to a higher chance of transmission of JEV to mosquitoes, animals, and human population in Sarawak.

Some JE cases in Malaysia have prompted researchers to have a rethink about the transmission of JE in humans. An outbreak reported in Pulau Langkawi was surprising; there were neither pig farms in these areas nor other amplifying agents. Typically, common animals like cattle, water buffalo, cats and dogs where are not considered as amplifying host in the transmission of JEV, so the source of the virus remains unknown. Another case reported in Tanah Merah, Kelantan in 2006 also led to questions about JE transmission in this area. There were no pig farms in this area. However, there were paddies developing in the area which can lead to a higher chance of breeding mosquitoes but without the possibility of JEV transmission by the mosquitoes.

It is important to study the role of bats in JEV in Malaysia. There has been no study of JEV in bats in Malaysia. Most studies concern cattle, horses, dogs, sheep, cats, goats, pigs, birds, wild boar and mosquitoes. Some studies indicated that bats may play an important role in the transmission of JEV since JEV is able to induce viremia as long 25–30 days at a level high and is able to cross the placenta of bats (Sulkin and Allen, 1974), and most tropical bats are able to travel less than 200 km during shifting season (Mackenzie et al., 2008). JEV has been isolated from bats of the families *Pteropodidae*, *Rhinolophidae*, *Hipposideridae*, and *Vestpertilionidae*. Some studies proved that mosquito-bat-mosquito transmission was successful at room temperature at 10 °C. This means that bats have high potential for JEV transmission besides pigs and wild boar in Malaysia (Mackenzie et al., 2008).

15. Conclusion

Japanese encephalitis is a major public health issue in Asian countries. Currently, JE is not considered as a major public health problem in Malaysia except Sarawak state where the mortality rate is 9%. Interestingly, most of the recent human JE cases in Malaysia were reported only among children as compared to JE cases in 40s–90s, which included infection of both adult and children by JEV. However, to date all the JE cases reported in children in Malaysia were mainly in Sarawak. The transmission of JE in Malaysia is less predictable due to some other ecological factors and environmental conditions that are contributing to JEV transmission in Malaysia. The route of transmission of JEV in Malaysia is still unclear and human JE cases are still being detected among children in peninsular Malaysia and Sarawak. Several animal species in Malaysia including cattle, dogs, cats, birds, pigs, horses and monkeys have been documented to possess JE antibodies. Even though pigs may play core role in transmission of JEV in Malaysia, some of the human JE cases were reported in areas without any pig farms, such as JE outbreak in Pulau Langkawi in 1974 and JE cases in Kelantan in 2006. In Sarawak, the human JE cases were reduced after introduction of JEV vaccination among children. This may be raising a strong surveillance with a good immunization program. Execution of a vaccination program for children as well as improved vector control, isolation of pig farms from paddy cultivation areas and residential areas, and agricultural activities can decrease JE cases in Malaysia. Although the JEV infection is not a critical issue in peninsular Malaysia, perhaps JEV is circulating among reservoirs especially bats, birds and other animals in peninsular Malaysia since there is reoccurrence of human JE cases every year.

Declaration of interest

None.

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References

Abu Hassan, A., Dieng, H., Satho, T., Boots, M., Al Sariy, J.S.L., 2010. Breeding patterns of the JE vector culex gelidus and its insect predators in rice cultivation areas of northern peninsular Malaysia. Trop Biomed. 27, 404–416.
Amal, N.M., Lye, M.S., Ksiazek, T.G., Kitsutani, P.D., Hanjeet, K.S., Kamaluddin, M.A., Ong, F., Devi, S., Stockton, P.C., Ghazali, O., Zainab, R., Taha, M.A., 2000. Risk factors for Nipah virus transmission, Port Dickson, Negeri Sembilan, Malaysia: results from a hospital-based case-control study. Southeast Asian J. Trop. Med. Public Health 31, 301–306.
Amerasinghe, F.P., Indrajith, N.G., 1994. Post irrigation breeding patterns of surface water mosquitoes in the Mahaweli project, Sri Lanka, and comparisons with preceding developmental phases. J. Med. Entomol. 31, 516–523.
Arkib Utusan Online, 2000. Veterinary Department May Declare Perak Free of JE and Nipah viruses by Year End. http://ww1.utusan.com.my/utusan/info.asp?y=2000&dt=0412&pub=Utusan_Express&sec=Home_News&pg=hn_09.htm Published 2000. (Accessed 10 March 2016).
Bamford, M., Watkins, D., Bancroft, W., Tischler, G., Wahl, J., 2008. Migratory Shorebirds of the East Asian Australasian Flyway; Population Estimates and Internationally Important Sites. Wetlands International Oceania, Canberra.
Bhattacharya, S., Basu, P., 2014. Japanese encephalitis virus (JEV) infection in different vertebrates and its epidemiological significance: a review. Int. J. Fauna Biol. Stud. 1, 32–37.
Bi, P., Tong, S., Donald, K., Parton, K.A., Ni, J., 2003. Climate variability and transmission of Japanese encephalitis in eastern China. Vector Borne Zoonotic Dis. 3, 111–115.
Bi, P., Zhang, Y., Parton, K.A., 2007. Weather variables and Japanese encephalitis in the metropolitan area of Jinan city, China. J. Infect. 55, 551–556.
Bowen, E., T, W., Simpson, D.I.H., Platt, G.S., Hilary, J.W., Bright, W.F., Day, J., 1975. Arbovirus infections in Sarawak, October 1966–February 1970: human serological studies in a Land Dyak Village. Trans. R. Soc. Trop. Med. Hyg. 69, 182–186.
Breed, A.C., Smith, C.S., Epstein, J.H., 2006. Winged wanderers: Long distance movements of flying foxes. In: Macdonald, D.W. (Ed.), The Encyclopedia of Mammals. Oxford University Press, Oxford, pp. 474–475.
Burke, D.S., Leake, C.J., 1988. Japanese encephalitis. In: Monath, T.P. (Ed.), The Arboviruses: Epidemiology and Ecology. CRC Press Inc., Florida, pp. 63–92.
Cardosa, M., Choo, B.H., 1991. A serological study of Japanese encephalitis virus infection in northern Peninsular Malaysia. Southeast Asian J. Trop. Med. Public Health 22, 341–346.
Cardosa, M.J., Hooi, T.P., Kaur, Pyar, 1995. Japanese encephalitis virus is an important cause of encephalitis among children in Penang. Southeast Asian J. Trop. Med. Public Health 26 (1991), 272–275.
Carey, D.E., Reuben, R., Myers, R.M., 1969. Japanese encephalitis studies in Vellore, South India, V. Experimental infection and transmission. Indian J. Med. Res. 57, 282–289.
Chanama, S., Sukprasert, W., Sa-ngasang, A., A-nuegoonpipat, A., Sangkitporn, S., Kurane, I., Anantapreecha, S., 2005. Detection of Japanese encephalitis (JE) virus-specific IgM in cerebrospinal fluid and serum samples from JE patients. Jpn. J. Infect. Dis. 58, 294.
Chu, M.M., 2014. Two Confirmed JE Cases in Penang Spark Fear of Another Outbreak Website. http://says.com/my/news/two-confirmed-je-cases-in-penang-spark-fear-of-another-outbreak.
Chua, K.B., 2003. Nipah virus outbreak in Malaysia. J. Clin. Virol. 26, 265–275.
Cruickshank, E.K., 1951. Acute encephalitis in Malaya. Trans. R. Soc. Trop. Med. Hyg. 45, 113–118.
Dhakal, S., Stephen, C., Ale, A., Joshi, D., 2012. Knowledge and practices of pig farmers regarding Japanese encephalitis in Kathmandu. Nepal. Zoonoses Public Health 59, 569–574.
Endy, T.P., Nisalak, A., 2002. Japanese encephalitis virus: ecology and epidemiology. Curr. Top. Microbiol. Immunol. 267, 11–48.
Erlanger, T.E., Weiss, S., Keiser, J., Utzinger, J., Wiedenmayer, K., 2009. Past, present, and future of Japanese encephalitis. Emerg. Infect. Dis. 15, 1–7.
Fang, R., Hus, Lim, T.W., 1980. Investigation of a suspected outbreak of Japanese encephalitis in Pulau Langkawi. Malays. J. Pathol. 3, 23–30.
Go, Y.Y., Balasuriya, U.B., Lee, C.K., 2014. Zoonotic encephalitides caused by arboviruses: transmission and epidemiology of alphaviruses and flaviviruses. Clin. Exp. Vaccine Res. 3, 58–77.
Hale, J.H., Witherington, D.H., 1953a. A serological survey of antibodies to Japanese B encephalitis virus among horses in Malaya. Ann. Trop. Med. Parasitol. 48, 15.
Hale, J.H., Witherington, D.H., 1953b. Encephalitis in racehorses in Malaya. Ann. Trop. Med. Parasitol. 63, 195–198.
Hale, J.H., Lim, K.A., Chee, P.H., 1952. Japanese type B encephalitis in Malaya. Ann. Trop. Med. Parasitol. 46, 220–226.
Hale, J.H., Colless, D.H., Lim, K.A., 1957. Investigation of the Malaysian form of culex tritaeniorhynchus as a potential vector of Japanese B encephalitis virus on Singapore Island. Ann. Trop. Med. Parasitol. 51, 17–25.
Hill, M.N., 1970. Japanese encephalitis in Sarawak: studies on adult mosquito

populations. Trans. R. Soc. Trop. Med. Hyg. 64, 489–496.
Hsu, S.M., Yen, A.M., Chen, T.H., 2008. The impact of climate on Japanese encephalitis. Infect. Ecol. Epidemiol. 136, 980–987.
Impoinvil, D.E., Solomon, T., Schluter, W.W., Rayamajhi, A., Bichha, R.P., Shakya, G., Caminade, C., Baylis, M., 2011. The spatial heterogeneity between Japanese encephalitis incidence distribution and environmental variables in Nepal. PLoS One 6, e22192.
Impoinvil, D.E., Baylis, M., Solomon, T., 2012. Japanese encephalitis: on the one health agenda. In: Mackenzie, J., Jeggo, M., Daszak, P., Richt, J. (Eds.), One Health: The Human-Animal-Environment Interfaces in Emerging Infectious Diseases Current Topics in Microbiology and Immunology. Springer, Berlin, pp. 205–247.
Impoinvil, D.E., Ooi, M.H., Diggle, P.J., Caminade, C., Cardosa, M.J., Morse, A.P., Baylis, M., Solomon, T., 2013. The effect of vaccination coverage and climate on Japanese encephalitis in Sarawak, Malaysia. PLOS Negl. Trop. Dis. 7, 1–9.
International Society for Infectious Diseases, 1998a. Japanese Encephalitis Malaysia. (accessed 12 March 2016). http://www.promedmail.org/.
International Society for Infectious Diseases, 1998b. Japanese Encephalitis, Suspected Malaysia. (accessed 12 March 2016). http://www.promedmail.org/.
International Society for Infectious Diseases, 1998c. Japanese Encephalitis Vaccinations, Malaysia. (accessed 10 March 2016). http://www.promedmail.org/.
International Society for Infectious Diseases, 1999a. Japanese Encephalitis - Malaysia (06). (accessed 12 March 2016). http://www.promedmail.org/.
International Society for Infectious Diseases, 1999b. Japanese Encephalitis - Malaysia: Update. (accessed 12 March 2016). http://www.promedmail.org/.
International Society for Infectious Diseases, 1999c. Japanese Encephalitis -Malaysia: Update. (accessed 12 March 2016). http://www.promedmail.org/.
International Society for Infectious Diseases, 1999d. Japanese Encephalitis - Malaysia (06). (accessed 11 March 2016). http://www.promedmail.org/.
International Society for Infectious Diseases, 1999e. Japanese Encephalitis - Malaysia: Update (02). (accessed 11 March 2016). http://www.promedmail.org/.
International Society for Infectious Diseases, 1999f. Japanese Encephalitis - Malaysia & Singapore. (accessed 14 March 2016). http://www.promedmail.org/.
International Society for Infectious Diseases, 2006. Japanese Encephalitis-Malaysia Kelantan. (accessed 13 March 2016). http://www.promedmail.org/.
International Society for Infectious Diseases, 2014. Japanese Encephalitis - Malaysia (02): Porcine, Human, Control. (accessed 13 March 2016). http://www.promedmail.org/.
Jabatan Perkhidmatan Veterinar, 2018. Perangkaan Ternakan 2016/2017 Website. (accessed 21 April 2017). http://www.dvs.gov.my/index.php/pages/view/1743.
Kabilan, L., Vrati, S., Ramesh, S., Srinivasan, S., Appaiahgari, M.B., Arunachalam, N., Thenmozhi, V., Kumaravel, S.M., Samuel, P.P., Rajendran, R., 2004. Japanese encephalitis virus (JEV) is an important cause of encephalitis among children in Cuddalore district, Tamil Nadu, India. J. Clin. Virol. 31, 153.
Kanojia, P.C., Geevarghese, G., 2004. First report on high-degree endophilism in culex tritaeniorhynchus (Diptera: culicidae) in an area endemic for Japanese encephalitis. J. Med. Entomol. 41, 994–996.
Karunaratne, S.H., Hemingway, J., 2000. Insecticide resistance spectra and resistance mechanisms in populations of Japanese encephalitis vector mosquitoes, culex tritaeniorhynchus and Cx. gelidus, in Sri Lanka. Med. Vet. Entomol. 14, 430–436.
Khan, S.A., Narain, K., Dutta, P., Handique, R., Srivastava, V.K., Mahanta, J., 1997. Biting behaviour and biting rhythm of potential Japanese encephalitis vectors in Assam. J. Infect. Dis. 29, 109–120.
Kheng, C.S., Chee, T.K., Marchette, N.J., Garcia, R., Rudnick, A., Coughlan, R.F., 1968. Japanese B encephalitis in a horse. Aust. Vet. J. 44, 23–25.
Kumar, K., Arshad, Siti Suri, Selvarajah, Gayathri Thevi, Abu, Jalila, Ooi, P.T., Abba, Yusuf, et al., 2017. Prevalence and risk factors of Japanese encephalitis virus (JEV) in livestock and companion animal in high-risk areas in Malaysia. Trop Anim Health Prod. 50, 741–752.
Leong, C.S., Vythilingam, I., Wong, M.L., Wan Sulaiman, W.Y., Lau, Y.L., 2018. Aedes aegypti(linnaeus) larvae from dengue outbreak areas in Selangor showing resistance to pyrethroids but susceptible to organophosphates. Acta Trop. 15, 115–126.
Low, V.L., Chen, C.D., Lee, H.L., Lim, P.E., Leong, C.S., Sofian-Azirun, 2013. Current susceptibility status of Malaysian culex quinquefasciatus (Diptera: culicidae) against DDT, propoxur, malathion, and permethrin. J. Med. Entomol 50, 103–111.
Lowry, P.W., Truong, D.H., Hinh, L.D., Ladinsky, J.L., Karabatsos, N., Cropp, C.B., Martin, D., Gubler, D.J., 1998. Japanese encephalitis among hospitalized pediatric and adult patients with acute encephalitis syndrome in Hanoi, Vietnam 1995. Am. J. Trop. Med. Hyg. 58, 324–329.
Luu, Y.M., 2014. Immunisation Schedule. My Health, Ministry of Health Malaysia. website. http://www.myhealth.gov.my/en/immunisation-schedule/.
Mackenzie, J.S., Johansen, C.A., Ritchie, S.A., van den Hurk, A.F., Hall, R.A., 2002. Japanese encephalitis as an emerging virus: the emergence and spread of Japanese encephalitis virus in Australasia. Curr. Top. Microbiol. Immunol. 267, 49–73.
Mackenzie, J.S., Williams, D.T., Smith, D.W., 2007. Japanese encephalitis virus: the geographic distribution, incidence, and spread of a virus with a propensity to emerge in new areas. Perspect. Med. Virol. 16, 201–268.
Mackenzie, J.S., Childs, J.E., Field, H.E., Wang, L.F., Breed, A.C., 2008. The role of bats as reservoir hosts of emerging neurological viruses. In: Reiss, C.S. (Ed.), Neurotropic Viral Infections. Cambridge University Press, United Kingdom, pp. 383–406.
Malay mail online, 2014. Sabah Health Department to closely monitor Japanese Encephalitis risk website. http://www.themalaymailonline.com/malaysia/article/sabah-health-department-to-closely-monitor-japanese-encephalitis-risk#DRQMUpWxWtRGPw28.97. (accessed 3 May 2016).
Masuoka, P., Klein, T.A., Kim, H.C., Claborn, D.M., Achee, N., Andre, R., Chamberlin, J., Small, J., Anyamba, A., Lee, D.K., 2010. Modeling the distribution of culex tritaeniorhynchus to predict Japanese encephalitis distribution in the Republic of Korea. Geospat. Health 5, 45–57.
Mitchell, C.J., Chen, P.S., Boreham, P.F.L., 1973. Host-feeding patterns and behaviour of 4 culex species in an endemic area of Japanese encephalitis. Bull. World Health Organ. 49, 293–299.
Mogi, M., 1983. Relationship between number of human Japanese encephalitis cases and summer meteorological conditions in Nagasaki. Jpn. Am. J. Trop. Med. Hyg. 32, 170–174.
Mwandawiro, C., Boots, M., Tuna, N., Suwonkerd, W., 2000. Heterogeneity in the host preference of Japanese encephalitis vectors in Chiang Mai, northern Thailand. Trans. R. Soc. Trop. Med. Hyg. 94, 238–242.
Ng, C.W., Choo, W.Y., Chong, H.T., Dahlui, Maznah, Goh, K.J., Tan, C.T., 2009. Long-term socioeconomic impact of the Nipah virus encephalitis outbreak in Bukit Pelanduk, Negeri Sembilan, Malaysia: a mixed methods approach. Neurol Asia 14, 101–107.
Nur Aqidah Azizi, 2016. Negri Sembilan Records Third Japanese Encephalitis Case. https://www.nst.com.my/news/2016/06/152076/negri-sembilan-records-third-japanese-encephalitis-case.
Oda, K., Igarashi, A., Kheong, C.T., Hong, C.C., Vijayamalar, B., Sinniah, M., Hassan, S.S., Tanaka, H., 1996. Cross-sectional serosurvey for Japanese encephalitis specific antibody from animal sera in Malaysia 1993. Southeast Asian J. Trop. Med. Public Health 27, 463–470.
Ohno, Y., Sato, H., Suzuki, K., Yokoyama, M., Uni, S., Shibasaki, T., Sashika, M., Inokuma, H., Kai, K., Maeda, K., 2009. Detection of antibodies against Japanese encephalitis virus in raccoons, raccoon dogs and wild boars in Japan. J. Vet. Med. Sci. 71, 1035–1039.
Okuno, T., Okada, T., Kondo, A., Suzuki, M., Kobayashi, M., Oya, A., 1968. Immunotyping of different strains of Japanese encephalitis virus by antibody-absorption, haemagglutination-inhibition and complement-fixation tests. Bull. World Health Organ 38, 547–563.
Paily, K.P., Chandhiran, K., Vanamail, P., Pradeep Kumar, N., Jambulingam, P., 2013. Efficacy of a mermithid nematode romanomermis iyengari (Welch) (Nematoda: Mermithidae) in controlling tree hole-breeding mosquito Aedes albopictus (Skuse) (Diptera: Culicidae) in a rubber plantation area of Kerala, India. Parasitol. Res. 112, 1299–1304.
Paterson, P.Y., Ley, H.L.Jr., Wisseman, C.L.Jr., Pond, W.L., Smadel, J.E., Diercks, F.H., Hetherington, H.D.G., Sneath, P.H.A., Witherington, D.H., Lancaster, W.E., 1952. Japanese encephalitis in Malaya. L isolation of virus and serological evidence of human and equine infections. Am. J. Trop. Med. Hyg. 66, 320–330.
Paz, S., 2015. Climate change impacts on West Nile virus transmission in a global context. Philos. Trans. R. Soc. Lond. B Biol. Sci. 370 (1665), 20130561.
Peiris, J.S.M., Amerasinghe, F.P., Arunagiri, C.K., Perera, L.P., Karunaratne, S.H.P.P., Ratnayake, C.B., Kulatilaka, T.A., Abeysinghe, M.R.N., 1993. Japanese encephalitis in Sri 464 Lanka: comparison of vector and virus ecology in different agro-climatic areas. Trans. R. Soc. Trop. Med. Hyg. 87, 541–548.
Philander, S.G.H., 1990. El Nino, La Nina, and the Southern Oscillation. Academic Press, San Diego, CA.
Pond, W.L., 1963. Arthropod-borne virus antibodies in Sera from residents of South-East Asia. Trans. R. Soc. Trop. Med. Hyg. 57, 364–371.
Pond, W.L., Russ, S.B., Lancaster, W.E., Audy, J.R., Smadel, J.E., 1953. Japanese encephalitis in Malaya, II Distribution of neutralizing antibodies in man and animals. Am. J. Trop. Med. Hyg. 17–25.
Reisen, W.K., Milby, M.M., 1986. Population dynamics of some Pakistan mosquitoes: changes in adult relative abundance over time and space. Ann. Trop. Med. Parasitol. 80, 53–68.
Reuben, R., 1971. Studies on the mosquitoes of North Arcot District, Madras State, India. 6. Seasonal prevalence of the culex vishnui group of species. J. Med. Entomol. 8, 367–371.
Reuben, R., Thenmozhi, V., Samuel, P.P., Gajanana, A., Mani, T.R., 1992. Mosquito blood feeding patterns as a factor in the epidemiology of Japanese encephalitis in southern India. Am. J. Trop. Med. Hyg. 46, 654–663.
Richards, E.E., Masuoka, P., Brett-Major, D., Smith, M., Klein, T.A., Kim, H.C., Anyamba, A., Grieco, J., 2010. The relationship between mosquito abundance and rice field density in the Republic of Korea. Int. J. Health Geogr. 9, 32.
Ricklin, M.E., García-Nicolás, O., Brechbühl, D., Python, S., Zumkehr, B., Nougairede, A., Charred, R.N., Posthaus, H., Oevermann, A., Summerfield, A., 2016. Vector-free transmission and persistence of Japanese encephalitis virus in pigs. Nat. Commun. 7, 10832.
Rivero, A., Vezilier, J., Weill, M., Read, A.F., Gandon, S., 2010. Insecticide control of vector-borne diseases: when is insecticide resistance a problem? PLoS Pathog 6 (8), e1001000.
Rodrigues, F.M., Vidyasagar, J., Singh, P.B., Ghosh, S.N., Guttikar, S.N., Joshi, M.V., Gupta, N.P., 1976. The 1973 epidemic of Japanese encephalitis in West Bengal: a serological survey of domestic animals. Indian J. Med. Res. 64, 973–980.
Rosen, L., 1986. The natural history of Japanese encephalitis virus. Annu. Rev. Microbiol. 40, 395–414.
Saito, M., Nakata, K., Nishijima, T., Yamashita, K., Saito, A., Ogura, G., 2009. Proposal for Japanese encephalitis surveillance using captured invasive mongooses under an eradication project on Okinawa Island. Jpn. Vector Borne Zoonotic Dis. 9, 259–266.
Schuh, A.J., Li, L., Tesh, R.B., Innis, B.L., Barrett, A.D., 2010. Genetic characterization of early isolates of Japanese encephalitis virus: genotype II has been circulating since at least 1951. J. Gen. Virol. 91, 95–102.
Schuh, A.J., Ward, M.J., Leigh Brown, A.J., Barrett, A.D.T., 2013a. Phylogeography of Japanese encephalitis virus: genotype is associated with climate. PLOS Negl. Trop. Dis. 7, e2411.
Schuh, A.J., Guzman, H., Tesh, R.B., Barrett, A.D., 2013b. Genetic diversity of Japanese encephalitis virus isolates obtained from the Indonesian archipelago between 1974 and 1987. Vector Borne Zoonotic Dis. 13, 479–488.

Sejvar, J., 2007. Emerging infections: the long-term outcomes of human: West Nile virus infection. Clin. Infect. Dis. 44, 1617–1624.

Siang, 1999. Chua Jui Meng Should Stop Making Malaysia a Laughing Stock and Publicly Acknowledge That the Outbreak in Bukit Pelanduk is Due Solely to the Hendra-like Virus and not JE. (accessed 4 May 2018). https://limkitsiang.com/archive/1999/apr99/sg1721.htm.

Simpson, D.I.H., Smith, C.E.G., Bowen, E.T.W., Piatt, S., Way, H., McMahon, D., Bright, W.F., Hill, M.N., Mahadevan, S., MacDonald, W.W., 1970a. Arbovirus infections in Sarawak: virus isolations from mosquitoes. Ann. Trop. Med. Parasitol. 64, 137–151.

Simpson, D.I.H., Bowen, E.T.W., Platt, G.S., Way, H., Smith, C.E.G., 1970b. Japanese encephalitis in Sarawak: virus isolation and serology in a Land Dyak village. Trans. R. Soc. Trop. Med. Hyg. 64, 503–510.

Simpson, D.I.H., Smith, C.E., Marshall, T.F., Platt, G.S., Way, H.J., Bowen, E.T., Bright, W.F., Day, J., McMahon, D.A., Hill, M.N., Bendell, P.J., Heathcote, O.H., 1976. Arbovirus infections in Sarawak: the role of the domestic pig. Trans. R. Soc. Trop. Med. Hyg. 70, 66–72.

Sinniah, M., 1989. A review of Japanese-B virus encephalitis in Malaysia. Southeast Asian J. Trop. Med. Public Health 20, 581–585.

Smith, C.E., 1958. The distribution of antibodies to Japanese encephalitis, dengue, and yellow fever viruses in five rural communities in Malaya. Trans. R. Soc. Trop. Med. Hyg. 52, 237–252.

Sulkin, S.E., Allen, R., 1974. Virus infections in bats. Monogr. Virol. 8, 1–103.

Sumodan, P.K., Vargas, R.M., Pothikasiorn, J., Sumanrote, A., Robin, R.L., Dujardin, J.P., 2015. Rubber plantations in Thailand and their mosquito fauna. In: Serge, M., Jean-Pierre, D., Lefait-Robin, R., Apiwathnasorn, C. (Eds.), Socio-Ecological Dimensions of Infectious Diseases in Southeast Asia. Springer Science Business Media, Singapore, pp. 155–170.

Takahashi, M., 1976. The effects of environmental and physiological conditions of culex tritaeniorhynchus on the pattern of transmission of Japanese encephalitis virus. J. Med. Entomol. 13, 275–284.

Tan, L.H., 1995. Japanese encephalitis in Malaysia. Southeast Asian J. Trop. Med. Public Health 26, 31.

Tangena, J.A.A., Thammavong, P., Wilson, A.L., Brey, P.T., Lindsay, S.W., 2016. Risk and control of mosquito-borne diseases in Southeast Asian rubber plantations. Trends Parasitol. 32, 402–415.

Thammapalo, S., Wonghiranrat, W., Moonmek, S., Sriplong, W., 2009. Biting time of Aedes albopictus in the rubber plantations and the orchards, the southern-most of Thailand. .J. Vector Borne Dis. 6, 1–6.

Tiawsirisup, S., Junpee, A., Nuchprayoon, S., 2012. Mosquito distribution and Japanese encephalitis virus infection in a bat cave and its surrounding area in Lopburi Province, Central Thailand. Thai. J. Vet. Med. 42, 43–49.

Ting, S.H., Tan, H.C., Wong, W.K., Ng, M.L., Chan, S.H., Ooi, E.E., 2004. Seroepidemiology of neutralizing antibodies to Japanese encephalitis virus in Singapore: continued transmission despite abolishment of pig farming? Acta Trop 92, 187–191.

Tipayamongkholgul, M., Fang, C.T., Klinchan, S., Liu, C.M., King, C.C., 2009. Effects of the El Nino-southern oscillation on dengue epidemics in Thailand, 1996– 2005. BMC Public Health 9, 422.

Vythilingam, I., Singh, K.I., Mahadevan, S., Zaridah, M.S., Ong, K.K., Abidin, M.H., 1993. Studies on Japanese encephalitis vector mosquitoes in Selangor, Malaysia. J. Am. Mosq. Control Assoc. 9, 467–469.

Vythilingam, I., Oda, K., Tsuchie, H., Mahadevan, S., Vijayamalar, B., 1994. Isolation of Japanese encephalitis virus from culex sitiens mosquitoes in Selangor, Malaysia. J. Am. Mosq. Control Assoc. 10, 228–229.

Vythilingam, I., Oda, K., Chew, T.K., Mahadevan, S., Vijayamalar, B., Morita, K., Tsuchie, H., Igarashi, A., 1995. Isolation of Japanese encephalitis virus from mosquitoes collected in Sabak Bernam, Selangor, Malaysia in 1992. J. Am. Mosq. Control Assoc. 11, 94–98.

Vythilingam, I., Oda, K., Mahadevan, S., Abdullah, G., Thim, C.S., Hong, C.C., Vijayamalar, B., Sinniah, M., Igarashi, A., 1997. Abundance, parity, and Japanese encephalitis virus infection of mosquitoes (Diptera: Culicidae) in Sepang District, Malaysia. J. Med. Entomol. 34, 257–262.

Wacharapluesadee, S., Samseeneam, P., Phermpool, M., Kaewpom, T., Rodpan, A., Maneeorn, P., Srongmongkol, P., Kanchanasaka, B., Hemachudha, T., 2016. Molecular characterization of Nipah virus from pteropus hypomelanus in Southern Thailand. Virol. J. 13, 53.

Wang, H.Y., Takasaki, T., Fu, S.H., Sun, X.H., Zhang, H.L., Wang, Z.X., Hao, Z.Y., Zhang, J.K., Tang, Q., Kotaki, A., Tajima, S., Liang, X.F., Yang, W.Z., Kurane, I., Liang, G.D., 2007. Molecular epidemiological analysis of Japanese encephalitis virus in China. J. Gen. Virol. 88, 885–894.

Wang, J.L., Pan, X.L., Zhang, H.L., Fu, S.H., Wang, H.Y., Tang, Q., Wang, L.F., Liang, G.D., 2009. Japanese encephalitis viruses from bats in Yunnan. China. Emerg. Infect. Dis. 15, 939–942.

Wang, C., Gourley, S.A., Liu, R., 2014. Delayed action insecticides and their role in mosquito and malaria control. J. Math. Biol 68, 417–451.

Wong, S.C., Ooi, M.H., Abdullah, A.R., Wong, S.Y., Krishnan, S., Tio, P.H., Pek, P.C., Lai, B.F., Mohan, A., Muhi, J., Kiyu, A., Arif, M.T., Cardosa, M.J., 2008. A decade of Japanese encephalitis surveillance in Sarawak, Malaysia: 1997-2006. Trop. Med. Int. Health 13, 52–55.

World Health Organization, 2017. Japanese Encephalitis Reported Cases. (accessed 10 May 2017). http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencejapenc.html.